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Serial No. 08/459,141  
Filed: 2 June 1995

AUG 15 2003

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overpayment to Deposit Account No. 06-1300 (Our File A-54528-9/DAV/DCF).

**AMENDMENTS**

In the Claims

21 2A9. (Amended) A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein the truncated polypeptide is a derivative of a herpes glycoprotein.

**REMARKS**

Initially, Applicants appreciate the Examiner's indication that claims 2, 6-8, 14 and 15 are allowed. Claims 1-15 are pending. Claims 1-15 have been renumbered by the Examiner. Claim 9 has been amended to recite "in vivo". Support is found at least at p. 21, lines 19-23, and p. 28, lines 18-22. For the Examiner's convenience a copy of the currently pending claims is appended hereto.

Response to Rejections

Claims 1, 3-5 and 9-13 are rejected under 35 USC § 112, first paragraph "because the specification, while being enabling for a method of immunizing an individual against herpes simplex 1 or 2 comprising administering a vaccine comprising a truncated, membrane free glycoprotein D polypeptide of herpes simplex virus, does not reasonably provide enablement for a method of immunizing against all pathogens or a method of immunizing against herpes simplex virus comprising administering a composition which comprises a membrane free derivative of a membrane bound protein, a truncated membrane-free derivative of a membrane-bound polypeptide or

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membrane bound polypeptide other than glycoprotein D". Mester, et al. Rev. Inf. Dis., 13 (supp 11); S935-S945 (1991) is cited in support of this rejection. Applicants respectfully traverse.

Initially, Applicants respectfully note that the claims are not drawn to a method of immunizing; rather, Claims 1 through 9 are drawn to vaccines comprising truncated, membrane-free derivative of a membrane-bound polypeptide. Claims 10 through 15 are drawn to a method of producing a vaccine.

Applicants respectfully submit that one of ordinary skill in the art at the time of filing of the application from which this case descends upon reading the present application would have a reasonable expectation of success in practicing the claimed invention. In support of this, Applicants note that at the time the present invention was filed in 1983, surface antigens from herpes virus were known. What was not known until the present invention, was that such antigens could be produced as vaccines as claimed (Claims 1-9) so as to be capable of raising neutralizing antibodies against in vivo challenge by a Herpes virus. The present application provides for the first time that such vaccines (in accordance with the claims) can be produced.

Thus, in 1983, it was a groundbreaking discovery that the present invention provided. Prior to the invention there was no teaching of a vaccine comprising polypeptides capable of raising neutralizing antibodies against in vivo challenge by herpes simplex virus type 1 and/or type 2. That is, there was a need in the field for improved vaccines. This was true of polypeptides comprising a truncated, membrane-free derivative of a membrane-bound polypeptide (claim 1 and 9). The present invention solved that problem. That is, despite the need in the field, for improved vaccines and methods of making vaccines, only following the filing and indeed the publication of the present

application was there widespread acceptance of the claimed vaccines and methods. Applicants note that the corresponding European application was published in May, 1985 (EP00139417); furthermore, much of the present work was published in *Science* in March 1985 (Berman et al. *Science* 1985 Mar 22;227(4693):1490-1492). Accordingly, Applicants submit that the specification indeed supports the scope of the present claims.

In support for Applicants position are a number of publications that were published after the filing and publication of the first application from which the present application descends; they are relevant for the following reasons:

1. The studies make clear that several different HSV glycoproteins are immunogenic and effective vaccines; a fact that also is supported in the specification of the application.
2. The studies demonstrate that vaccines as claimed are effective against in vivo challenge by Herpes virus.
3. The studies also demonstrate the widespread acceptance of the claimed method. That is, although the studies were published after the priority date and publication of the present application, several of them use vaccines and methods of preparing vaccines as described in the present claims.

Initially, Applicants note Ghiassi, et al., *J. Virol.*, 68(4):2118-2126 (1994) (Exhibit A), which was published after the filing and publication of the first application from which the present application descends. This reference was submitted in the Response to Office Action of October 22, 1997 in the present case, and is re-submitted herein.

While the study claims to be the first to express many herpes glycoproteins in baculovirus so that large quantities of the glycoproteins can be produced for study, the study makes clear that all of the glycoproteins which are being reported on have previously been studied and shown to be immunogenic, (page 2123, left column, first line of the second full paragraph). (Of note, of the "previous studies" which are referenced in Exhibit A, is a paper by Berman, (reference 4), the first named inventor of the present invention). Thus, Exhibit A demonstrates that after the filing and publication of the present application those skilled in the art can perform the claimed invention.

Furthermore, Ghiasi *et al.* (*Vaccine*, 1996, 14:107-112 (Exhibit B)) demonstrate that a combination of individually expressed HSV-1 glycoproteins conferred protection against HSV-1-induced eye disease.

Applicants further submit that the specification is enabling for vaccines and methods of making vaccines comprising polypeptides other than glycoprotein D from HSV type 1 or type 2. Applicants respectfully point to the specification, for example, at page 5, lines 5-14 wherein it is described that glycoproteins including HSV-1 gC, HSV-2 gF or combinations of the two proteins, or gA, gB, and gE can be formed. Furthermore, at page 6, line 23 the specification describes that terms HSV-2 gF, HSV-2 gC and gC-2 are used to refer to a glycoprotein portion of HSV-2 which is highly homologous with HSV-1 gC which is capable of raising sufficient antibodies to be useful as a vaccine. Thus, the specification provides support for vaccines in addition to glycoprotein D from HSV type 1 or type 2. Accordingly, Applicants submit that one of ordinary skill in the art upon reading the present specification, would be enabled in practicing the invention as claimed.

As for Claims 10 through 15, Applicants respectfully submit that the specification is

clearly enabling for a method of producing a vaccine as described in the claims. That is, the present invention, for the first time, enabled the skilled artisan to produce in a convenient manner, vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide. While the specification is replete with disclosure related to methods for preparing the secreted form of gD protein, Applicants submit that one of ordinary skill in the art could follow these teachings to prepare a vaccine based on a membrane protein of any organism. Furthermore, as described at p. 34, lines 4-10, "The success of this invention ... indicates that similar results can be expected with other immunogenic membrane bound proteins, thus providing an improved source of vaccine against viruses, parasites and other pathogenic organisms."

The Office Action has stated that while the specification shows homologies between gC and gF, there is no correlation with other Herpes glycoproteins and gD. Applicants respectfully submit that there is. In this regard, the assertions made by Applicants in the specification have been confirmed by others after the filing and publication of the present application.

Specifically, regarding glycoproteins other than gD, Applicants submit herein a review that describes different HSV vaccines (Bernstein and Stanberry, Vaccine 17 :1681-1689 (1999 (Exhibit C)). As noted at p. 1684, second column, second paragraph, the rationale for choosing surface glycoproteins as immunogens relates to the observation that they are the dominant target for antibody production in HSV infected people. Furthermore, as noted at p. 1684, second column, third paragraph, the expression of recombinant gB and gD "was improved by the insertion of truncated viral genes into mammalian expression vectors engineered so that the anchor portion of the protein was deleted [44,49]. In this way, mammalian cells can be engineered to synthesize a glycosylated HSV glycoprotein that is secreted."

In addition, Applicants respectfully note Exhibit D (Peng et al., J. Virol. 72: 65-72 (1998)) that describes a vaccine comprising secreted gH/gL complex and secreted gD of HSV. Furthermore, at p. 71, first column, first full paragraph, it is noted that "immunization with either gD or gHt-gL gave excellent protection ... These data... are the most encouraging results seen to date regarding the potential efficacy of gHt-gL as a vaccine." Again, this reference demonstrates how subsequent researchers have successfully applied the teachings of the present invention to produce vaccines comprising membrane-bound proteins or derivatives of membrane-bound proteins in accordance with the present claims.

Applicants note that Exhibit E (Nesburn et al., Investigative Ophthalmology & Visual Science 39:1163-1170 (1998)) indicates that secreted gD was used for immunization against HSV, in particular ocular HSV. The preparation of immunogen was prepared "as previously used by Chiron Corporation (Emeryville, CA) in clinical trials measuring protection from HSV-2 infection. Herpes simplex virus-1 glycoprotein D (gC1) was identically prepared at Chiron" (see "Glycoproteins for Vaccination" p. 1164, second column). Thus, the method of preparing a vaccine comprising secreted gD of HSV has found widespread use following Applicants' invention.

Moreover, Applicants respectfully draw attention to the Declarations that have been previously submitted during the prosecution of this case and in the case from which the present application descends. Specifically, in U.S. application serial no. 08/171,858 filed December 21, 1993, an amendment was mailed by Applicants dated July 21, 1994 with appendices including: 1) a declaration of John K. Rose in support of a reply to opposition by Chiron Corporation; 2) a (follow up) declaration of John K. Rose, Ph.D.; and 3) a statutory declaration by David S. Secher. These declarations were submitted in the present case in the Response to Office Action mailed February 5, 1997. For the

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Examiner's convenience, copies of these declarations are enclosed herein as Exhibits F, G and H, respectively. Applicants again note that these declarants are not inventors of the present invention and in fact, Dr. Rose is an author of one of the publications that was cited against the present application.

In the declaration of John K. Rose in Support of Reply to Opposition by Chiron Corporation, paragraph 8 states:

"one of ordinary skill in the art could not have predicted that a successful vaccine that raises neutralizing (protective) antibodies against in vivo challenge by a pathogen could have been produced based essentially on a truncated membrane-free derivative of a membrane-bound glycoprotein of the virus. . ."

It is clear based on this language that declarant viewed the invention as deriving from a glycoprotein, not limited to glycoprotein D.

Paragraph 9 of the same Declaration goes on to state:

"Based on this pioneering demonstration with the herpes simplex vaccine model, their results provide a reasonable expectation that the system would be successful with other viral pathogens."

Applicants again note that Dr. Rose clearly states that this "system would be successful with other viral pathogens". Applicants additionally note the term "pioneering" which indicates that Dr. Rose envisioned ground breaking and broad applications with this system. Applicants, therefore again submit that the Declaration supports the enablement of the invention.

In Paragraph 6 of the (follow-up) declaration of John K. Rose, Ph.D., Dr. Rose offers further explanation of the declaration discussed above. Specifically, Dr. Rose refers to the invention as providing "protection against the pathogen based solely on a truncated,

membrane-free derivative of a viral glycoprotein," indicating that one skilled in the art does not consider the invention limited to glycoprotein D or a specific pathogen. Moreover, in paragraph 13 of this declaration, Dr. Rose explains that any reasonable expectations of success in using the disclosed system arose because the inventors "demonstrated that all of the technical challenges to successful vaccine production had been overcome". Applicants, therefore, submit that this declaration supports the claimed invention.

Paragraph 11 of the statutory declaration by David S. Secher states:

"the scientific strength of this research resides in the use of a truncated version of a single glycoprotein from the rather complex model Herpes Simplex virus to confer protective immunity in the animal against the pathogen."

Applicants point out that like Dr. Rose, Dr. Secher did not mention the use of glycoprotein D but rather refers generally to a truncated version of a glycoprotein. Applicants therefore submit that this declaration supports the full scope of the presently claimed invention.

Thus, in contrast to the statement in the Office Action that the specification lacks sufficient guidance and teaching to enable the entire scope of the claims, Applicants submit that the declarations and references submitted herein fully support the entire scope of the claims. Accordingly, Applicants submit that the specification is enabling for the entire scope of the claims.

Applicants respectfully point out that an Applicants' specification that discloses information on how to make and use the invention must be accepted unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. If the Patent Office does present doubt to the accuracy of the disclosure, then such a rejection can



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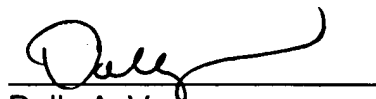
be overcome by suitable proofs such as the submission of expert declarations. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). If, arguendo, the Patent Office has shown reason to doubt the accuracy of the disclosure, Applicants have met their burden of proof for enablement by providing an enabling disclosure, and further by providing "suitable proofs" that confirm the statements in the disclosure. Applicants, therefore, respectfully request that this rejection be withdrawn.

### **CONCLUSION**

Applicants submit that the claims are now in condition for allowance and an early notification of such is solicited. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Pending claims:

1. A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein the truncated polypeptide is a derivative of a glycoprotein of a herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex type 1 and/or type 2.
2. A vaccine according to Claim 1 wherein the truncated polypeptide is a derivative of a glycoprotein D.
3. A vaccine according to Claim 1 wherein the truncated polypeptide is a derivative of a glycoprotein C.
4. A vaccine according to Claim 1 wherein the truncated polypeptide is a derivative of a glycoprotein C of a herpes simplex virus type 1 and/or type 2.
5. The vaccine according to Claim 1 wherein said polypeptide comprises a mixture of glycoproteins.
6. The vaccine according to Claim 5 in which said mixture comprises glycoprotein C and glycoprotein D.
7. The vaccine according to Claim 5 wherein said mixture comprises glycoprotein D.
8. The vaccine according to Claim 7 wherein said mixture further comprises glycoprotein B.
9. (Amended) A vaccine comprising a truncated, membrane-free derivative of a membrane-bound polypeptide, said derivative being devoid of membrane-binding domain whereby the derivative polypeptide is free of said membrane, and having exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein the truncated polypeptide is a derivative of a herpes glycoprotein.
10. A method of producing a vaccine according to any one of Claim 1, 2, 3 or 4 wherein DNA encoding said membrane-bound polypeptide is prepared lacking coding for membrane-binding domain, incorporating the DNA into an expression vector, transfecting a host cell with said vector, and collecting the truncated polypeptide as a secretion product.
11. A method according to Claim 10 wherein the transfected host cell is a stable eukaryotic cell line.
12. A method according to Claim 11 wherein the transfected host cell is a mammalian cell line.
13. A method according to Claim 11 or Claim 12 wherein the cell line is deficient

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in the production of dhfr and the vector contains a dhfr selectable marker.

14. A method according to Claim 10 wherein the truncated polypeptide is a glycoprotein D of herpes simplex virus type 1 or type 2.

15. A method according to Claim 14 wherein the truncated polypeptide is restricted to the first 300 amino acid residues of the glycoprotein D.

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